Guidance for Industry

ANDAs: Blend Uniformity Analysis

DRAFT GUIDANCE

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For questions on the content of the draft document contact Devinder S. Gill, 301-827-5848.

U.S. Department of Health and Human Services
Food and Drug Administration
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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

ANDAs: Blend Uniformity Analysis[2]

I. INTRODUCTION

This guidance is intended to provide recommendations to applicants of abbreviated new drug applications (ANDAs) on establishing in-process acceptance criteria for blend uniformity analysis (BUA).[3] This guidance provides recommendations on when BUA should be performed and how to perform BUA. The recommendations apply to original ANDAs and supplemental ANDAs for formulation and process changes.

FDA's regulations state that the information submitted to support applications must include in-process controls for the drug products (21 CFR 314.50(d)(1)(ii)(a) and 314.94(a)(9)(i)). The Center for Drug Evaluation and Research (CDER) guidance for industry on *Submitting Documentation for the Manufacture of and Controls for Drug Products* (February 1987) states that "the analytical controls used during the various stages of manufacturing and processing of the dosage form should be fully described. Where feasible, the in-process specifications should be supported by appropriate data that can include, but should not be limited to, representative master/batch production and control records." BUA is an in-process test that is useful for ensuring the adequacy of the mixing of active pharmaceutical ingredients (APIs) with other components of the drug product. The in-process testing requirement for adequacy of mixing to ensure uniformity and homogeneity is established at 21 CFR 211.110(a)(3).

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[1] This guidance has been prepared under the direction of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on blend uniformity analysis for ANDAs. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] The primary application of this guidance is expected to be in the manufacture of solid oral dosage forms, although certain other dosage forms are covered by the document. To simplify the document, blend uniformity analysis has been discussed in this guidance in the context of solid oral dosage products. The principles discussed in this guidance apply equally to other types of blends and dosage forms.

[3] An earlier guidance entitled *Submitting Documentation for the Manufacture of and Controls for Drug Products* (February 1987) is currently being revised. When that document is finalized, the contents of this guidance will eventually be incorporated and extended, as appropriate, to new drug applications (NDAs).

Recommendations are provided in this guidance on the following:

- BUA testing for certain dosages, based on their composition, according to strength (mg of active) and weight to weight percent (w/w% of the active)
- Sample size and procedures
- Acceptance criteria for blend uniformity analysis

FDA intends to seek the support of the Product Quality Research Institute on blend uniformity. This guidance will be updated based on the outcome of any research.

II. SCOPE

BUA is recommended for those drug products for which the U.S. Pharmacopeia (USP) requires content uniformity analysis. USP requires this test when the drug product contains less than 50 milligrams of the active ingredient per dosage form unit, or when the active ingredient is less than 50 percent of the dosage form unit by weight. BUA is recommended for bioequivalence, test, and commercial production batches of a drug product.

BUA or homogeneity testing can be applied to all dosage forms, but is recommended for those dosage forms for which the USP requires content uniformity testing. These dosage forms include:[4]

- Coated tablets, other than film coated tablets
- Transdermal systems
- Suspensions in single-unit containers or in soft capsules
- Pressurized metered-dose inhalers
- Suppositories

If the composition of the drug product is greater than or equal to 50 milligrams of the active ingredient per dosage form unit or the active ingredient is greater than or equal to 50 percent of the dosage form unit by weight, blend uniformity analysis is not usually necessary (see Attachment A). For complex dosage forms, such as modified-release tablets or capsules, and complex processes (e.g., multistep granulation processes), applicants are advised to consult the appropriate

[4] USP 23, Supplement 7, <905>, Uniformity of Dosage Units.

chemistry reviewing division to determine if BUA is recommended (see Attachment B).

Under current good manufacturing practices (CGMPs), an applicant is required to perform a test or examination on each commercial batch of all products to monitor the output and validate the performance of processes that could be responsible for causing variability, which includes adequacy of mixing to ensure uniformity and homogeneity (21 CFR 211.110(a)(3)). A BUA test for commercial batches in an approved application meets this requirement. An applicant should not submit a supplemental application requesting the deletion of BUA testing from commercial batches when the BUA test is also used to ensure compliance with CGMPs. A supplement requesting deletion of BUA testing should include supportive information justifying that the test would not be considered necessary under CGMPs. Requests for deletion of BUA testing as an approved in-process specification do not relieve a firm of its responsibilities for compliance with CGMPs. Where an approved application does not include a BUA for commercial batches, conformance with the CGMP requirement will be evaluated under the drug CGMP regulatory program.

III. SAMPLING SIZE AND PROCEDURES

The recommended sample size of the blend material is no more than three times the weight of an individual dose. If the firm experiences problems in collecting small samples equivalent to 1 to 3 dosage units and demonstrates that small samples give lower values for BUA due to sampling bias, larger samples (usually no more than 10 dosage units) can be collected. Justification for larger samples should be specific to the application under review. Justification based on literature references is usually not adequate.

Samples for BUA can be collected either from the drums or the blenders. For more than one drum or blender, analysis from each drum or blender is encouraged for the bioequivalence and/or test batches. The batch size, number of samples (usually 6 to 10), locations of sampling, and equipment should be specified as part of the in-process controls for BUA or homogeneity. Potential differences in mixing efficiency associated with specific types of equipment should be considered when determining sampling locations.

BUA is recommended for all active ingredients present in the drug product. Since the purpose of BUA is to assess the uniformity and homogeneity of a blend, composite sampling from various sites is not appropriate. The weight of the sample tested should be equivalent to the dosage used.

If a common blend is used for the manufacture of multiple strengths of the drug product, the weight of the sample used should be equivalent to the weight of the lowest strength of the drug product. For a drug product where different strengths are not made from the same common

blend, BUA for each blend is recommended.

IV. ACCEPTANCE CRITERIA AND ANALYTICAL PROCEDURES

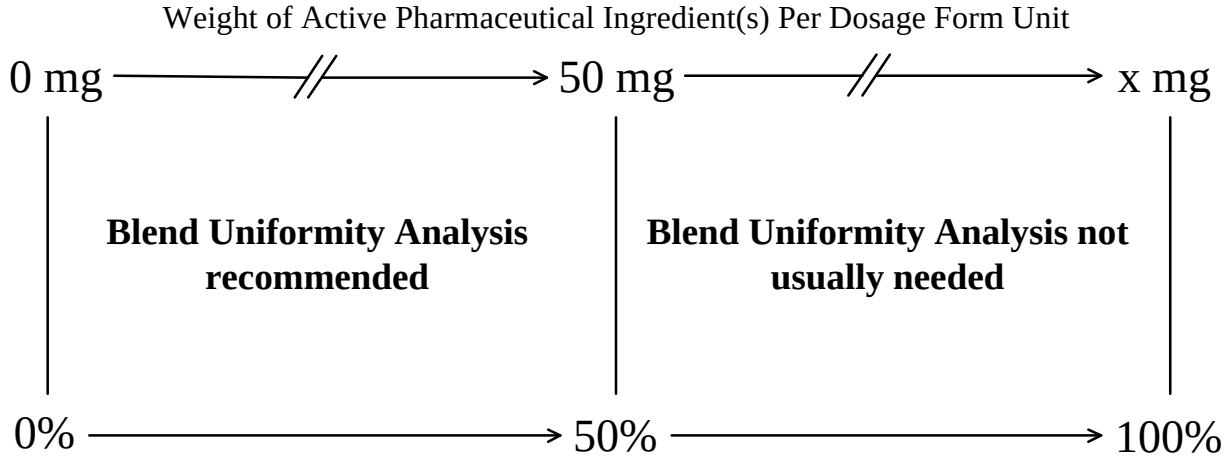
Manufacturing records for bioequivalence batches, test batches, and commercial production batches for drug products for which BUA is recommended should include documentation of test results and acceptance criteria for BUA. Analytical procedures for BUA can be described separately in the section of the ANDA application (Section XII) on in-process controls.[5]

Acceptance criteria of 90.0 percent to 110.0 percent of the expected quantity of active ingredient (mean of individual test results) with a relative standard deviation (RSD) of no more than 5.0 percent are recommended for BUA. This will allow compensation for any potential loss in blend uniformity during subsequent manufacturing steps and also ensure compliance with USP acceptance criteria for content uniformity. The BUA results should be reported as individual test results, mean value, and calculated RSD. Rounding of BUA results to whole numbers is not recommended. Additional levels of testing through the use of two-tier acceptance criteria are also not recommended.

[5] See the FDA guidance for industry on *Organization of an ANDA* (February 1999).

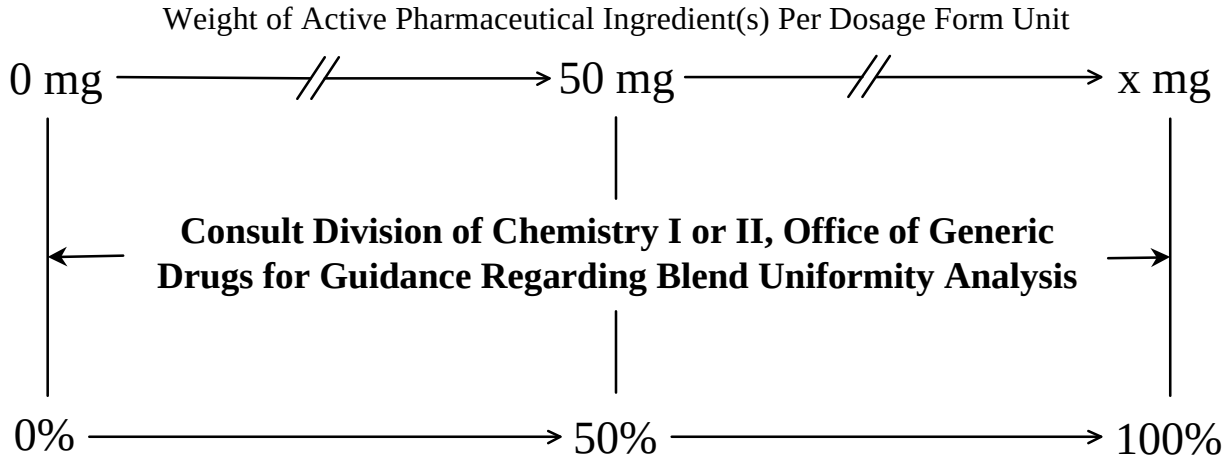
ATTACHMENT A

Blend Uniformity Analysis Recommendations for Simple Dosage Forms



ATTACHMENT B

Blend Uniformity Analysis Recommendations for Complex Dosage Forms and Complex Processes



GLOSSARY

Acceptance Criteria: Acceptance criteria are numerical limits or other suitable measures for acceptance of the results of analytical procedures.

Active Pharmaceutical Ingredient/Drug Substance: The active pharmaceutical ingredient or drug substance is the ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body (21 CFR 314.3).

Batch: A batch is a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture (21 CFR 210.3(b)(2)).

Drug Product: A drug product is a finished dosage form (e.g., a tablet or capsule that contains a drug substance) generally, but not necessarily, in association with one or more other ingredients (21 CFR 214.3).

In-Process Controls: In-process controls are tests that can be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests that are conducted prior to release (ICH draft guidance Q6A, Step 2).

In-Process Material: In-process material is any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)).